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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/616,247	07/14/2000	Dennis A. Carson	30448.80USD2	6658

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EXAMINER	
SHAHNAN SHAH, KHATOL S	
ART UNIT	**PAPER NUMBER**
1645	

DATE MAILED: 08/13/2002 11

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/616,247	CARSON ET AL.	
	Examiner	Art Unit	
	Khatol S Shahnan-Shah	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the c rrespondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 April 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *10 and 18-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10 and 18-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Applicants' reply and Amendment received April 29, /2002, paper 9 is acknowledged. Claim 24 was amended. Claims 12 and 25-31 were cancelled.

2. Currently claims 10,and 18-24 are pending and under consideration.

Prior Citations of Title 35 Sections

3. The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior office action.

Prior Citations of References

4. The references cited or used as prior art in support of one or more rejections in the instant office action have been previously cited and made of record. No form PTO-892 has been submitted with this office action.

Priority

5. This application filed under former 37 CFR 1.62 lacks the necessary reference to the prior application. The priority statement entered following the title of the invention or as the first sentence of the specification is incomplete; applicants need to update the status of parent applications.

Specification

6. The disclosure is objected to because of the following informalities:
Specification page 17, line 18 there are blank spaces for an application serial number and filing date.

Appropriate correction is required.

Rejection Withdrawn

7. Rejection of claims10 and 18-24 under 35 U.S.C. 112 second –paragraph made in paragraph 7 of the office action mailed December 19, 2001 (paper number 8) is withdrawn in view of the applicants' amendment and arguments.

Rejection Maintained

8. Rejection of claims10 and 18-24 under 35 U.S.C. 112 first –paragraph made in paragraph 6 of the office action mailed December 19, 2001 (paper number 8) is maintained.

The rejection was as stated below:

Claims 10 and 18-24 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to a DNA composition useful in inducing immune protection against arthritogenic peptides in a host comprising a recombinant gene expression vector which encodes bacterial dnaJp1 peptide. The specification is not enabled for a DNA composition useful in inducing immune protection against arthritogenic peptides in a host comprising a recombinant gene expression vector, which encodes bacterial dnaJp1 peptide.

The specification discloses various in vitro experiments that demonstrate antibody binding to rdnaJ, inhibition studies and binding of rdnaJ to lympohcytes from patients with RA, however the specification does not teach a skilled artisan how to administer the claimed composition for immune protection. The specification presents a paper protocol in this regard. The specification has not taught a skilled artisan how to use the invention as presently claimed.

Applicants have not shown or disclosed a correlation between in vitro and in vivo studies or that there are animal models that correlate to human (i.e. person) efficacy.

The specification fails to provide an enabling disclosure for the preparation and use of a DNA composition, including expression vector compositions comprising nucleic acids encoding antigens because it fails to provide adequate guidance regarding how one would have prepared a nucleic acid which when introduced into a host would induce an immune response against the protein encoded by said nucleic acid. In contrast to direct protein immunogens, nucleic acids are required to target appropriate cell types within a host, become transcriptionally active, appropriately process any encoded proteins and present such proteins to the host in a manner suitable for recognition by the host's immune system. Such a **"gene therapy"** approach to epitope delivery suffers from all the limitations associated with gene therapy technology. However, as of 12/95, the artisan did not accept, in the absence of suitable and particular guidance, that such could have been accomplished without having had to exercise undue experimentation. See e.g. NIH Report Reference.

Applicants' specification fails to provide guidance to the skilled artisan on the parameters for DNA vaccine for the breadth of the claimed invention. Numerous factors complicate the gene therapy art, which have not been shown to be overcome by routine experimentation. These include, the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the

protein's compartmentalization within the cell, or its secretory fate, once produced. These factors differ dramatically based on the vector used, the protein being produced, and the disease being treated.

Additionally, the specification does not provide any working examples which enable the claimed invention. Nor does the specification provide any guidance to the skilled artisan on how to make and use genetic constructs which would result in the desired effect. Even assuming that an effective genetic material is constructed, it is not evident that enough cells can be transfected to provide any therapeutic benefit.

Several recent reviews indicate that efficient delivery and expression of foreign DNA has not yet been achieved by any method. Marshall (*Science*, 269:1050-1055, August, 1995) states that "there has been no unambiguous evidence that genetic treatment has produced therapeutic benefits" (page 1050, column 1) and that "difficulties in getting genes transferred efficiently to target cells- and getting them expressed- remain a nagging problem for the entire field" (page 1054, column 3). James Wilson, one skilled in the art, is quoted in the Marshall article as saying that "'[t] he actual vectors- how we're going to practice our trade- haven't been discovered yet" (page 1055, column 2). Miller et al (*FASEB J.*, 9:190-199, 1995) also review the types of vectors available for *in vivo* gene therapy, and conclude that "for the long-term success as well as the widespread applicability of human gene therapy, there will have to be advances...targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (page 198, column 1). Therefore, even if the specification enabled the construction of the gene delivery vehicle

comprising a cell targeting element, in the absence of particular guidance, the artisan would have been required to develop *in vivo* and *ex vivo* means of practicing the claimed methods and such development in the nascent and unpredictable gene therapy art would have been considered to have necessitated undue experimentation on the part of the practitioner.

Furthermore the art teaches that EBV is possibly the cause of RA (col. 3, l. 4-14) and the administration of anti-inflammatory agents, not the virus itself (cols. 4-6) (Carson 5,310,732 and Carson et al. WO 90/14835). Hyman discloses that RA may be caused by a bacterial source, bacteria are associated with RA (col. 5), however they do not suggest or use bacterial polynucleotides in a vaccine preparation for administration to induce immune protection to treat RA in a person. Rather Hyman uses antibiotics effective against the bacteria and additional antibiotics such as kanamycin or neomycin for example (col. 27; claims). It is unclear from the art what is the etiological cause of RA, and therefore would be unclear and an undue burden to a skilled artisan to determine what type of composition to administer to a person with RA to reduce its exposure or predisposed to develop RA. Should antibiotics, anti-inflammatory agents, or EBV or some bacterial protein or nucleic acid be administered to stimulate an immune response or some combination of the above? In view of the reasons set forth, there would be undue experimentation for a skilled artisan to practice the claimed invention.

A disclosure in an application, to be complete, must contain such description and details as to enable any person skilled in the art or science to which it pertains to make and use the invention as of its filing date, In re Glass, 181 USPQ 31; 492 F2.d 1228 (CCPA 1974). While the prior art setting may be mentioned in general terms, the essential novelty, the essence of the invention, must be described in such details, including proportions and techniques where

necessary, as to enable those persons skilled in the art to make and utilize the invention.

Applicants' arguments filed 4/29/2002 have been fully considered and are not persuasive. Applicants argue that the specification teaches preparation of the claimed composition and in support of applicants' position (Exhibit A), La Cava, et al. J. Immunology 164 (3): 1340-5 is submitted. Applicants' argue that La Cava, et al. confirm that one skilled in the art would have been able to and use the composition of the invention. Applicants further argue that it is noted that, while La Cava, et al. was published in February 2000, it recognized that later publications can be used as evidence of the state of the art existing at the time of filing of an application. It is the examiner's position to agree with applicants in regard to the issue of that later publications can be used as evidence of the state of the art existing at the time of filing of an application. However the examiner respectfully disagrees with the applicants that La Cava, et al. confirm that one skilled in the art would have been able to and use the composition of the invention.
It is also the examiner's that the state of the art even 4-6 years after the claimed invention is unpredictable. La Cava et al recite" After intradermal genetic immunization, naked DNA is transported from the site of injection to regional lymph nodes. Little is known on how inflammation influences this process and whether DNA is transported beyond the local lymph nodes" or " Additional studies are required to address this possibility and the relevance of this pathway to chronic inflammation associated with infection". See La Cava et al abstract and discussion, pages 1340, 1343-1344).

The claims are broadly drawn to a composition useful in inducing immune protection against arthritogenic peptides in a host comprising a recombinant gene expression vector which encodes bacterial dnaJp1 peptide. The specification fails to provide an enabling disclosure for the

preparation and use of a DNA composition, including expression vector compositions comprising nucleic acids encoding antigens because it fails to provide adequate guidance regarding how one would have prepared a nucleic acid which when introduced into a host would induce an immune response against the protein encoded by said nucleic acid.

Applicants further argue that guidance was provided in detail in pages 14-18 of the specification in selection of polynucleotides, vectors and necessary material. The examiner respectfully disagrees and brings applicants attention to page 17, line 18 of the specification as to the fact that applicants are discussing modified vectors which are useful in gene immunization protocols and incorporate a copending application by reference. However the patent application number and filing date have left blank. The examiner can not evaluate applicants arguments based on those issues.

Conclusion

9. No claims are allowed.

10. THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Khatol Shahnan-Shah whose telephone number is (703) 308-8896. The examiner can normally be reached on 7:30 AM - 4 PM from Monday through Friday. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette F Smith, can be reached on (703) 308-3909. The fax phone number for the organization where this application or proceeding is assigned to is (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

8/7/02

Khatol Shahnan-Shah, BS, Pharm, MS

Biotechnology Patent Examiner

Art Unit 1645

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